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14. ABSTRACT

A major gap in understanding of blast TBI is how external kinetic blast energy translates to pressure transients in the brain. This project used miniaturized pressure sensors engineered at the LLNL to measure immediate increases in intracranial pressure (ICP) combined with longer-term measurements of biological ICP. We found that the existing LLNL sensors were not capable of measuring pressure changes in a wet environment. We solved this problem by enclosing a reference volume over the sensor diaphragm which provided reliable measurements over a range of pressures. We found that the brain responded differently to sensors implanted for 14 days in the rats cranial vault at different locations and that epidural sites minimized brain cell death and glial scarring. Static and dynamic pressure tests of the modified sensors reliably measured pressure transients in a test chamber connected to the fluid percussion device. The modified sensors reliably detected pressure transient in the brain of rats subjected to fluid percussion TBI. Modifications to the circuitry of the sensors provided accurate and reliable measures of temperature within a physiological range. A limitation was revealed that the sensor could not detect small pressure changes associated with biological ICP and will require further engineering and fabrication.

15. SUBJECT TERMS
BI, sensors, pressure, brain, temperature

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1. **INTRODUCTION:**
The major objective of this research effort was to create new sensing technologies and perform preliminary studies prior to rapid transition to testing in blast TBI models. This project proposed to use miniaturized, state-of-the-art pressure/temperature sensors engineered at LLNL to measure the immediate increases in ICP combined with longer-term measurements of biological ICP and intracranial temperature. The experience gathered from this seed proposal provided valuable data on sensor placement, long-term brain tissue responses to implanted sensors, and sensor capability of dual measurement of biologic ICP and impact pressure transients that will be directly applicable to subsequent transition into blast TBI animal models.

2. **KEYWORDS:** TBI, pressure, temperature, sensors, ICP

3. **OVERALL PROJECT SUMMARY:**
Year 2 funding:
Task 3: (optional year effort): To implement multi-modality micro sensors (evaluated in Funding year 1) in a large animal model of blast TBI.

In our final report at the conclusion of our year 1 funding we stated that:

> "A shortcoming of the modified sensors was the inability to measure very low pressures associated with biological ICP from brain edema (less than 1 psi). Engineering calculations indicate that a thinner sensor diaphragm will make such small pressure measurements feasible without compromising high pressure measurements associated with blast TBI. The third generation sensors are planned to be designed and fabricated for the option year of this project."

Dr. Kotovsky at LLNL has been diligently re-engineering the previous sensor by designing a new 3rd generation sensor to address the shortcomings described above. Dr. Kotovsky has made advancements in design and fabrication of the sensors such that we should be able to produce a better product with superior capabilities. We have also been very prudent in our expenditures and have retained sufficient funds to complete the original deliverables. Thus, while the delays in progress have been frustrating, we feel confident that we will be able to complete the objectives and deliverables during the 12-month no-cost extension period and with a better product.

Drs. Lyeth and Kotovsky continued to have regular monthly phone conferences to discuss plans for moving the project forward.

Dr. Kotovsky has met June, 2013 with the director of US sales for the company we will purchase wafers from for the new sensor chip build. Dr. Kotovsky is now organizing the geometries to be included in that build. Those wafers will be processed at Sandia National Laboratories and at the wafer thinning house for the process development and chip build. The wafer purchase will include additional wafers needed for the development work. A quote for this work has been received and we will place the order once our design geometry is complete. This requires coordination with Sandia as their silicon patterning stepper drives some of the geometry choices for the build.

We are in discussions with a sub-contractor in Livermore who will perform the packaging assembly work. Dr. Kotovsky is working with the sub-contractor now on practice assemblies anticipating the new upcoming build. Working through an outside contractor represents an enormous cost savings for this fabrication work versus performing that work at LLNL. In the future, that company may also serve as a supplier for sensors to Walter Reed and other organizations.

We have also discussed the process development risks with the wafer lapping company. The proposed change in the process to create buried diaphragms for TBI pressure sensing places the wafer at risk of mechanical failure. Dr. Kotovsky has discussed these risks with the lapping vendor and believes we have a good chance of success but this remains our greatest risk.

4. KEY RESEARCH ACCOMPLISHMENTS:

Nothing to report.

5. CONCLUSION:

In the remaining time of our current no-cost extension, we plan to have the newly designed 3rd generation sensor chips fabricated and in-hand and then packaged (encased) for in vivo animal use. We will then proceed to test the prototypes in the engineering laboratory prior to moving to our in vivo rat TBI model for practical testing. Specifically, the 3rd generation sensors will incorporate modifications to produce greater accuracy and reliability in measurements of biological ICP. We also plan to further refine the sensors into a smaller overall package and to design and implement a more user-friendly connection between the sensor and the recording instruments in order to make a smooth transition into making measurement in a swine blast TBI model later on in the project.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Nothing to report.

7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:

Nothing to report.

9. OTHER ACHIEVEMENTS:

Nothing to report.

10. REFERENCES:

None

11. APPENDICES:

Nothing to report

14. ABSTRACT:

Background: Explosion or blast is the most common cause of injuries in the Iraq and Afghanistan wars. Non-penetrating traumatic brain injury (TBI) from blasts and explosions, referred to as blast TBI, are a significant source of morbidity in the Mideast war theater. A major gap in the understanding of blast TBI is how external kinetic energy from a blast event translates to pressure transients in the brain, how long these transients last, and how they propagate through the cortical matter. Furthermore, what is the relationship between these pressure changes and tissue damage? Only a limited number of studies to date have examined rapid pressure changes in the brain from exposure to blast.

Objective/Hypothesis: The major objective of this project is to create new sensor technologies and perform preliminary studies in an impact model of TBI for subsequent rapid transition to testing in blast TBI models with future funding opportunities. The hypothesis is that measurement of intracranial pressure transients in an impact model of traumatic brain injury will provide valuable data about sensor performance within a biological system that will be directly applicable to subsequent transition into blast TBI animal models.

Specific Aims:
1) To evaluate existing prototype micro pressure sensors from Lawrence Livermore National Laboratories (LLNL) in a rat impact TBI model.
2) To design and evaluate second generation LLNL multimodal micro pressure sensors (shock wave, biological ICP, and temperature) in a rat impact TBI model.
3) (option year effort) To implement multi-modality micro sensors (evaluated in Task 2) in a swine model of blast TBI.

Study Design: This seed project proposes to use miniaturized, state-of-the-art pressure/temperature sensors engineered at the LLNL to measure the immediate increases in intracranial pressure (ICP) combined with longer-term measurements of biological ICP and intracranial temperature. Experiments will utilize the placement of multiple sensors at strategic locations within the calvarium in order to obtain the most rigorous measure of acute transmission of pressure waves through the brain, and reflection/rebound pressure waves within the cranium as well as longer-term changes in biological ICP, and intracranial temperature.

Relevance: Current sensor technology developed at LLNL is capable of measurement of rapid pressure changes following blast injury, but has not yet been tested within a biological system (e.g., mammalian brain).
Successful implementation of this technology in a well-characterized impact TBI model will allow rapid and efficient translation of the sensor technology to future studies with collaborators utilizing swine and non-human primate models of blast TBI. With the large number of troops sustaining some form of concussive brain injury, the need for increased understanding of the consequences of blast on brain biology is critical for the development of therapeutic strategies to treat these casualties as well as for the redesign of protective gear.